DRAFT

LAW OFFICES OF
SKJERVEN, MORRILL, MacPHERSON, FRANKLIN & FRIEL
25 Metro Drive, Suite 700
San Jose, California 95110
(408) 453-9200

TWX No. 9103382094
Telecopy No. (408) 453-7979

FACSIMILE MESSAGE TRANSMITTAL FORM GROUP 1800

TO: Examiner Margaret Moskowitz Parr
Group 1800
U.S Patent and Trademark Office
Washington, D.C. 20231

FROM: Laura Terlizzi, Esq.

CLIENT/FILE #: M-1647-6C US

SUBJECT: U.S. Patent Application entitled:
"INTRON SEQUENCE ANALYSIS METHOD FOR DETECTION OF ADJACENT AND REMOTE LOCUS ALLELES AS HAPLOTYPES"
Serial No.: 07/949,652
Filing Date: September 23, 1992
Inventor: Malcolm J. Simons
Applicant: GeneType AG
Our Reference: M-1647-6C US

Facsimile No.: (703) 308-4227
Number of Pages: 9 (total)
Date Sent: March 6, 1995

Phone No.: (703) 308-2454
Sent By: P.Ray
Time Sent: 2:45

Message:

Enclosed is an informal communication regarding the matter we discussed in a telephone conversation on March 3, 1995. Please call me if I can be of assistance in this matter.

Laura Terlizzi

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LAW OFFICES OF
SKJERVEN, MORRILL, MacPHERSON, FRANKLIN & FRIEL

M E M O R A N D U M

TO: Examiner Margaret Moskowitz Parr
U.S. Patent and Trademark Office

FROM: Laura Terlizzi

RE: Telephone Conference of March 3, 1995 between Examiner Parr and Laura Terlizzi regarding the following case:

Applicant: Malcolm J. Simons
Assignee: GeneType AG
Title: "INTRON SEQUENCE ANALYSIS METHOD FOR DETECTION OF ADJACENT AND REMOTE LOCUS ALLELES AS HAPLOTYPES"
Serial No.: 07/949,652 Filed: September 23, 1992
Examiner: Bradley L. Sisson Group Art Unit: 1807
Attorney Docket No.: M-1647-6C US

DATE: March 6, 1995

The application we discussed is identified above.

BRIEF HISTORY OF THE STATUS OF THE PROSECUTION OF THE PARENT APPLICATION

Issues at the Close of Prosecution of the Parent Application

As we discussed, this application is a continuation of U.S.S.N. 07/551,239, now U.S. Patent No. 5,192,659, issued March 9, 1993. As you recall, I had a personal interview with you and Examiner Yuan which was followed by allowance of the application with claims limited to analysis of HLA loci. At the interview, you believed that there was insufficient evidence that the analysis method would work for genetic loci generally as it was exemplified in the HLA loci, a highly polymorphic group of human genes that are driven to diversity.

The claimed analysis method is based on Dr. Simons' discovery that non-coding region polymorphisms were informative and can be used to determine alleles and haplotypes of linked genetic loci. At the close of prosecution of the parent application, you stated that you would consider declarations from experts as to whether such informative polymorphisms were present throughout the genome. The

experts needed to present the reasons why the data they described demonstrated that such polymorphisms were generally present and not limited to human genes or to polymorphic or highly polymorphic loci.

Declarations Submitted to Overcome the Overbreadth Rejection

Three expert declarations were submitted in this application. The first (submitted with a Preliminary Amendment on January 14, 1993) was by Professor Peter Gresshoff, one of the Declarants in the parent application. Professor Gresshoff was sequencing an intergenic region near the soybean supernodulation (NTS) locus, a plant locus which is believed to be conserved. Professor Gresshoff stated that the soybean NTS gene region exhibited the same kind of polymorphism as the HLA loci. More specifically, Professor Gresshoff found sequence heterogeneity in a one kilobase intergenic region where restriction endonuclease digestion revealed no differences in the sequences of the region. He also determined that some of these intergenic region non-coding sequence polymorphisms were indicative of the soybean cultivar from which the DNA sample was taken.

This data convinced Professor Gresshoff that the phenomenon that non-coding region sequences contain informative polymorphisms that can be used to identify associated coding region alleles is a general phenomenon. Professor Gresshoff explicitly stated that he believes that the "the basis for Malcolm Simons' analysis system applies to all eukaryotic genomes".

The second Declaration was by Dr. Leroy Hood and was submitted September 24, 1993. Dr. Hood stated that he sequenced a 100 kilobase region of the Alpha Delta T-cell receptor gene in both mouse and man. The homology between mouse and man for those genes was approximately 70%. Dr. Hood stated that that is approximately the homology many coding regions between mouse and man exhibit. Yet 95% of the sequenced region was non-coding. He considered this observation "a great surprise".

Dr. Hood also stated that Malcolm Simons' data demonstrates that the percentage of homology of non-coding regions and of coding regions in different alleles of the HLA loci is approximately the same. Dr. Hood stated "[t]he data demonstrated that relatively short non-coding region sequences contained informative polymorphisms which can be used as the basis of an HLA typing system". (page 1) Dr. Hood also reviewed Professor Gresshoff's Declaration regarding the NTS gene. Dr. Hood stated that Dr. Hood's data demonstrated a similar phenomenon between genes of species which diverged approximately seventy to eighty million years ago and that this phenomenon is particularly striking in the T-cell receptor gene which is a paradigm of the diversity genes. Dr. Hood concluded:

> The HLA data and the NTS data indicate the presence of informative polymorphisms in non-coding regions in these vastly different types of genes from species that diverged tens of millions of years ago. In addition, the type of homology I found in sequencing non-coding regions of mouse and man in the Alpha Delta T-cell receptor is consistent with these findings. Therefore, I believe that informative polymorphisms which are indicative of linked alleles and haplotypes are present throughout the eukaryotic genome. (page 2)

The final declaration was by Dr. Pablo Rubinstein. Dr. Rubinstein reviewed a number of recent articles by authors unrelated to Dr. Malcolm Simons, the inventor of this application, or to GeneType AG, the assignee of the application. Dr. Rubinstein stated that the articles "demonstrate that the allelic variants of coding regions are accompanied by concordant variants of adjacent non-coding regions of diverse non-HLA genes". (page 2) Dr. Rubinstein further stated that "[t]his feature of allelic variation is thus found in systems with limited polymorphism in humans and also in other mammals and even in insects". (page 2)

Dr. Rubinstein described each of the articles and stated that the articles each relate to non-coding region polymorphisms that are indicative of coding region alleles. The articles described genes as diverse as the alcohol dehydrogenase ADH-71k gene in Drosophila, human tumor necrosis factor and aldolase B (causing fructose intolerance) genes, and the casein gene in cattle. Dr. Rubinstein concluded:

> In view of the generality of the phenomenon in so varied a group of genes and species, one would expect that any polymorphic genetic locus would have correlated variation in its coding and non-coding regions. (page 3)

It is believed that each of the Declarations contain facts that demonstrate that relatively short non-coding region sequences contain informative polymorphisms that can be used to determine alleles and haplotypes of adjacent loci generally and overcome the remaining rejection at the close of prosecution of the parent application.

SUMMARY OF THE PROSECUTION OF THE PRESENT APPLICATION

Prosecution under the Prior Examiner

In a first Office Action in this application, Examiner Tran presented a number of 35 U.S.C. § 112, first paragraph rejections based on lack of enablement and indefiniteness. In addition, the Declaration of Professor Gresshoff was rejected for containing "newly introduced matter." Claims 17-20 were rejected under 35 U.S.C. § 103 over references cited in the parent application.

An amendment addressing the rejections and including the Declaration of Dr. Hood was filed September 24, 1993. In response, an Office Action indicating that, with the exception of Claims 17-20, 35, 36, and 38, all of the claims were allowed was mailed December 13, 1993. In response, the non-allowed claims were canceled without prejudice to renewal in an amendment filed December 22, 1993.

Prosecution under Examiner Sisson

Applicant's Attorney had a telephonic interview with Examiner Sisson on January 7, 1994, in which Examiner Sisson stated that the case had been transferred and prosecution on the merits was reopened. Applicant's Attorney discussed the case in general terms with the Examiner at that time. In the Office Action mailed January 13, 1994, Examiner Sisson indicated that all claims were rejected and stated that Claims 17-20, 28-36, and 38 were canceled. However, the Amendment canceled Claims 17-20, 35, 36, and 38. In other words, rather than canceling Claims 35 and 36, Claims 28-36 were canceled.

The Office Action included a rejection of the claims for lack of support for including the term "non-coding" which term is present in the issued claims in the parent application. That rejection was withdrawn in the outstanding Office Action.

The Office Action also included a rejection of Claims 1-13, 15, 16, 37, and 39-41 under 35 U.S.C. §112, first paragraph, for lack of enablement. The basis of the rejection was that one of skill would not be able to determine how to practice the method, and, in particular, would not be able "to predetermine what types of primers (sequence length and composition) are to be used." In exemplifying the basis for this rejection, the Examiner stated that a "locus may well be comprised of a cluster of alleles" and referred to two of the HLA loci as exemplary.

In the response to this Office Action, Applicant's Attorney pointed out guidance in the specification and that the level of skill in designing primers is high. Applicant's Attorney also noted that claims related to analysis of the HLA loci have issued and therefore, there was no issue of whether one of skill could practice the method

by selecting appropriate primers at the close of prosecution of the parent application.

The second basis for the enablement rejection was said to be that "[t]he specification is not enabling for the generation and use of primers that would be of sufficient length such that they permit the spanning of virtually any intronic sequence". In addressing this rejection, Applicant's Attorney pointed out that the claim require only that the primers amplify a portion of a non-coding region sequence so that whether an intron was 200 nucleotides or 10 kilobasepairs in length was irrelevant.

An Amendment filed July 13, 1994, addressed the rejections as described above and included the Declaration of Dr. Pablo Rubinstein. The Amendment re-added the claims that had been canceled to obtain allowance of the application (Claims 17-20, 35, 36, and 38). In addressing the enablement rejection, Applicant's Attorney pointed out the prosecution history as described above and described that the only issue at the close of prosecution of the parent application was based on overbreadth due to an insufficient demonstration that the method would work outside the HLA loci. A explanation of how the three declarations overcame this basis for the rejection was presented.

THE OUTSTANDING OFFICE ACTION

Refusal to Enter Canceled Claims

In a Final Office Action mailed November 23, 1994, Examiner Sisson refused to enter "Claims 17-20 and 35-38", stating that Claims 1-16, 21-27, and 39-43 were pending. (This claim tally does not match the first page of the Office Action which indicates that Claims 1-16, 21-27, 37, and 39-43 are pending and Claims 17-20, 28-36 and 38 are canceled.) The reason given for refusing to enter the claims is described as follows:

> there appears a request for the entry of new claims 17-20 and 35-38. This portion of the amendment has NOT been entered as said claims have been previously canceled. (emphasis in original, page 2)

Applicant's Attorney believes it is inappropriate to refuse to enter claims in response to a non-final office action where the claims were only canceled to obtain allowance of the application and the allowability of the claims was withdrawn.

The Enablement Rejection

The 35 U.S.C. § 112, first paragraph, rejection was maintained for Claims 1-13, 15, and 16. The Examiner repeated both bases for the rejection. Specifically, the Examiner stated "the specification has not provided guidance as to how one is to predetermine what types of primers (sequence length and composition) are to be used" (page 3). The Examiner again stated:

> this aspect is further complicated when one considers that a given locus may well be comprised of a cluster of alleles (*exempli gratia* the HLA Class II locus DQA1 is comprised of 8 alleles and the DPB locus is comprised of 24 alleles). (page 3)

In addressing Applicant's Attorney's arguments, the Examiner stated "there is a low level of predictability of achieving a useful probe or primer". (page 4) Applicant's argument that issuing method claims for HLA loci indicated that the method was enabled for such loci was not addressed.

In maintaining the rejection due to the inability to amplify an intron of 10,000 bases, the Examiner stated:

> while the claims may well encompass the amplification of a part or portion of an intron, now a "non-coding region", the claims have sufficient breadth to encompass the spanning of the complete length of the intron/non-coding region, as well as additional sequences. The specification clearly does not enable the use of primers which allow for the amplification of such large sequences. (page 5)

As stated previously, that one cannot amplify large non-coding regions is irrelevant, since there is no need to do so to practice the claimed method.

Evaluation of the Declarations

Although Examiner Sisson reviewed each of the declarations, the Examiner appeared to evaluate the declarations to determine whether the declarations present:

> any evidence or suggestion that the specification as originally filed enables one of skill in the art to practice the claimed method in a generic manner where the primer pair spans a non-coding region that could be many kilobases in length,

> e.g., 10 kb, and simultaneously develop priers (*sic*, primers) that would allow for one of skill in the art to amplify any non-coding region sequence which is adjacent to an exon encoding the allele where the allele is part of a multi-allelic genetic locus. (page 6, regarding the evaluation of the Hood Declaration)

Therefore, it is clear that Examiner Sisson did not recognize the overbreadth rejection at the close of prosecution of the parent application and found the declarations non-persuasive because the declarations address whether the method is generally applicable and not whether one of skill could select primers to amplify informative polymorphisms in non-coding region sequences. This is believed to be an inappropriate basis for a rejection for at least four reasons. First, it is clear that the level of skill in the art is sufficient to select primers. Second, there is no need to amplify 10 kb regions since amplification of regions under 1 kb were sufficient to analyze the complex HLA loci. Third, such issues were not present at the close of prosecution of the parent application. Deference to the determinations in the parent application should be given. Fourth, the rejection calls into question the validity of the parent application since the rejection specifically relates to enablement of the method for the HLA Class II loci, which is within the scope of the issued claims.

In describing the Declaration of Dr. Hood, Examiner Sisson also stated:

> At page 2, second paragraph, Dr. Hood states: "My data demonstrated a similar phenomenon between genes of species which diverged approximately seventy to eighty million years ago", however, the declaration lacks any factual or evidentiary underpinning which would support the conclusory opinion being offered. (pages 6-7)

This and similar statements in telephonic interviews indicate that Examiner Sisson does not consider statements by Dr. Hood that he sequenced the genes and determined the stated percentage of homology believable in the absence of "factual or evidentiary underpinning which would support the conclusory opinion being offered". In discussing the Declaration, Applicant's Attorney stated that the percentage of homology was a fact. Examiner Sisson stated he wanted to know how the sequencing was performed and see the raw data to evaluate the statements made by Dr. Hood.

Dr. Hood is one of the best known experts in genetic research. There is no reason to question statements made by Dr. Hood because the Declaration does not contain raw data.

Double Patenting

The Office Action also included a new rejection for obviousness-type double patenting. The rejection is inappropriate since a Terminal Disclaimer was filed January 14, 1993.

I would be happy to provide any clarification of any issue or any further information that may be useful. I greatly appreciate your willingness to review the record and resolve these issues. Please call me at 408-283-1222, if I can be of any further assistance.